A functional genomics screen identifies an Importin-alpha homolog as a regulator of stem cell function and tissue patterning during planarian regeneration.

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Public Summary:
Studies of organisms that can regenerate have excellent potential to improve our understanding of how adult stem cells can be harnessed for therapeutic purposes. The goal of this work was to utilize planarian flatworms as models to gain insights into mechanisms regulating stem cell differentiation. We capitalized on the molecular tools available to study planarian regeneration to identify and functionally characterize genes with key roles in tissue repair, patterning and function. During the five-year funding period we completed high-throughput gene expression studies (microarray) using samples obtained from tissue replaced in the early phases of regeneration of the planarian head after amputation. We performed gene inhibition studies for hundreds of genes chosen from the microarray list based on expression pattern or homology. We identified 25 genes that were necessary for stem cell maintenance, general regenerative capability, or that caused tissue-specific defects upon knockdown. We also found that a homolog of the nuclear transport factor importin-alpha plays a role in stem cell function and tissue patterning, suggesting that controlled nuclear import of proteins is important for regeneration.

Scientific Abstract:
BACKGROUND: Planarians are renowned for their regenerative capacity and are an attractive model for the study of adult stem cells and tissue regeneration. In an effort to better understand the molecular mechanisms underlying planarian regeneration, we performed a functional genomics screen aimed at identifying genes involved in this process in Schmidtea mediterranea. METHODS: We used microarrays to detect changes in gene expression in regenerating and non-regenerating tissues in planarians regenerating one side of the head and followed this with high-throughput screening by in situ hybridization and RNAi to characterize the expression patterns and function of the differentially expressed genes. RESULTS: Along with five previously characterized genes (Smed-cycD, Smed-morf41/mrg-1, Smed-pdss2/dlp1, Smed-slbp, and Smed-tph), we identified 20 additional genes necessary for stem cell maintenance (Smed-sart3, Smed-smarcc-1, Smed-espl1, Smed-rrm2b-1, Smed-rrm2b-2, Smed-dkc1, Smed-emg1, Smed-lig1, Smed-prim2, Smed-mcm7, and a novel sequence) or general regenerative capability (Smed-rbap46/48-2, Smed-mcm2, Smed-ptbp1, and Smed-fen-1) or that caused tissue-specific defects upon knockdown (Smed-ddc, Smed-gas8, Smed-pgbd4, and Smed-b9d2). We also found that a homolog of the nuclear transport factor Importin-alpha plays a role in stem cell function and tissue patterning, suggesting that controlled nuclear import of proteins is important for regeneration. CONCLUSIONS: Through this work, we described the roles of several previously uncharacterized genes in planarian regeneration and implicated nuclear import in this process. We have additionally created an online database to house our in situ and RNAi data to make it accessible to the planarian research community.